REMARKS

The Invention.

The present invention provides truncated enzymes having deletions corresponding to a deletion of between 98 and 309 amino acids from the N-terminus of mature *Bacillus* pullulanase. The enzyme is required to retain a conserved Y region and also retain enzymatic activity.

Status of the Application.

Applicants acknowledge the acceptance of the RCE request for this application. Claims 5 - 10, 12, 14, 15, 27 - 40 and 52 - 66 are pending in the application. Claims 14, 39 and 40 have been amended to clarify what Applicants consider the invention. Claims 60-64 have been amended to be in compliance with 37 CFR §1.821(d). Applicants assert new matter has not been introduced by the amendment.

Sequence Compliance.

Claims 60-64 have been amended to recite SEQ ID NOs with the recited amino acid sequence. Specifically, the amino acid sequence VWAP (Val Trp Ala Pro) Is SEQ ID NO:9. Applicants believe that the cited claims are now in compliance with 37 CFR §1.821(d).

35 U.S.C. §112, first paragraph.

Claims 14 and 15 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification does not enable one skilled in the art to make the invention commensurate in scope with these claims. Applicants respectfully traverse.

Contrary to the Examiner's assertations, Applicants are not claiming any pullulanase. Applicants do not claim "a truncated pullulanase". Applicants claim "a truncated *Bacillus* pullulanase."

Although Applicants must respectfully disagree with the Examiner's argument and rationale, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments,

Applicants have amended Claim 14 to more clearly recite that the pullulanase is a *Bacillus* pullulanase.

For the foregoing reasons, Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §112, second paragraph.

Claims 39 and 40 are rejected under 35 USC §112, second paragraph as failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner asserts that the phrase "the modified pullulanase" was unclear. Applicants respectfully traverse.

Applicants have amended Claims 39 and 40 to recite "truncated pullulanase". Withdrawal of the rejection is respectfully requested.

35 U.S.C. §103.

The Examiner has rejected claims 5–7, 9-10, 14, 15, 27–29, 31–40, 52–53, 55-61 and 63–66 as allegedly obvious over the combination of Deweere, *et al.* (US Pat. No. 6,074,854) in view of McPherson *et al.* (Biochemical Soc. Trans., (1988) 16(5):723-724) and further in view of Albertson *et al.*, (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39). Applicants respectfully traverse the rejection.

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the references to arrive at the **claimed invention**. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

Deweer, et al. (US Pat. No. 6,074,854)

The Examiner cites Deweer *et al.* as teaching pullulanase from a Gram positive bacteria, methods of making the recombinant enzyme, compositions either in the solid or liquid form and compositions comprising additional enzymes. However, the Examiner

correctly recognizes that there is no teaching to modify the pullulanase by way of deletion of about 100, 200 or 300 N-terminal amino acids.

There is nothing in Deweer *et al.* that would motivate the skilled artisan to truncate the *Bacillus* pullulanase or to combine its teachings with McPherson *et al.* or Albertson *et al.*

McPherson et al. (Biochemical Soc. Trans., (1988) 16(5):723-724)

The Examiner cites McPherson *et al.* as teaching proteolytic digestion, computer-based sequence analysis, and that the long N-terminal region lacks any catalyzing site. See the paragraph bridging pages 7 and 8 of the Office Action.

The Examiner correctly notes that McPherson *et al.* is not teach a *Bacillus* pullulanase; it teaches a pullulanase from *Klebsiella pneumoniae,* a **gram-negative** rod-shaped bacteria. As further noted by the Examiner, McPherson *et al.* illustrates the relative position of 5 conserved regions with alpha-amylases from *Bacillus* or *Streptomyces*, both gram-positive organisms, or a fungus. McPherson *et al.* provides no comparison with a *Bacillus* pullulanase nor a suggestion that a pullulanase from a gram-positive organism shares similarity with a pullulanase from a gram-negative organism and that it would be similarly affected by truncation. Thus, McPherson *et al.* fails to suggest or motivate the skilled artisan to combine the teachings to obtain a truncated pullulanase from a *Bacillus* species.

The pullulanase taught by McPherson *et al.* demonstrated no extensive homology with other proteins. See page 723, column 1, second paragraph. The pullulanase of McPherson *et al.* has approximately 1100 amino acid residues. This is significantly larger than the 957 amino acid pullulanase from *B. deramificans* (including its signal sequence). Furthermore, the conserved "amylase" sequences are not provided by McPherson *et al.* so an alignment is not easily accomplished. Thus, Applicants contend the combination of references does not contain a sufficient teaching of how to obtain a truncated pullulanase from a *Bacillus* species.

Albertson et al., (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39)

The Examiner cites Albertson *et al.* (Cloning and sequence of a type I pullulanase from an extremely thermophilic anaerobic bacterium, Caldicellulosiruptor saccharolyticus. Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39) teaching the modification of a pullulanase isolated from *C. saccharolyticus*, wherein nearly 381 nucleotides from the 5' region of the cDNA encoding a pullulanase and that the deleted amino acid sequence is not essential for either activity or thermostability. See page 8 of the Office Action.

The enzyme most closely related to the pullulanase of *C. saccharolyticus* shares only about 35% identity with it. See page 36, column 2 of Albertson.

The truncated enzyme of Albertson has a truncation of 95 amino acids (see page 38, top of column 2) from its N-terminus, not the about 127 amino acids as predicted by the 381 nucleotide deletion as indicated by the Examiner. The 381 nucleotide deletion apparently is in reference to recombinant plasmid pNZ1038 which has non-coding sequences in the 5' region of the DNA fragment. Not only does this fail to suggest the required amino acid deletions but it also does not lead one of skill in the art to expect that larger deletions would be tolerated.

Albertson also purports to identify the conserved regions which define the enzymatically active portion of the enzyme (see page 38, column 2, first full paragraph). However, the present inventors have identified two further conserved sequences which extend further upstream of those identified in Albertson. These are the Y and VWAP regions, which indicate the limits of amino acid truncations in the N-terminal of pullulanases in general." This is described in the passage spanning pages 11 and 12 of the present application.

Albertson *et al.* fails to correct the deficiencies of either Deweer *et al.* or McPherson *et al.*

Thus, the present inventors have found, firstly, that significantly larger deletion mutants than that shown in the prior art are capable of retaining enzymatic activity. Secondly they have defined the maximum extent of such deletions which the enzyme can tolerate while retaining enzymatic activity. These findings are reflected in the claims as they now stand.

Applicants believe that, at best, the Examiner presents an "obvious to try" standard in determining the patentability of the present invention, a standard which has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 (Fed. Cir. 1989). Thus, Applicants respectfully request that the rejection be withdrawn and the Claims passed to allowance.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,
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